Renal function in hypoxaemic chronic obstructive pulmonary disease: effects of long-term oxygen treatment

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Abstract Impaired renal function is an important cause for the oedema formation, which often occurs in severe chronic obstructive pulmonary disease (COPD).

In the present study, the importance of nocturnal hypoxaemia (measured by a nocturnal pulse oximetry) for the renal function was determined in 19 COPD patients, with normal levels of serum creatinine. The effects on kidney function of alleviating the nocturnal hypoxaemia [using 6 months of long-term oxygen treatment (LTOT)], was assessed in 12 patients. Renal function was assessed by determining the clearances of intravenously administered inulin (C_{In}) and para-amino-hippurate (C_{PAH}) and orally supplemented lithium (C_{Li}) and of circulating sodium (C_{Na}). The 19 patients had a mean PaO_2 of 7.63 ± 1.08 kPa, a $PaCO_2$ of 5.98 ± 0.85 kPa, a mean nocturnal oxygen saturation ($MnSaO_2$) of 87.7 ± 2.8% and an FEV_1 in %P of 25.6 ± 14.6%. C_{In} and C_{PAH} were 35 and 45% lower than normal, respectively, whereas C_{In}/C_{PAH}=filtration fraction (FF) was 31% higher than normal. Six months of LTOT in 12 of the patients was not followed by any significant change in renal function in the entire study group. However, low pretreatment $MnSaO_2$ correlated with reductions in post-treatment (FF) (r=0.73, $P<0.05$). Post-treatment $PaCO_2$ did not change significantly in patients treated with oral diuretics, but increased ($P<0.05$) in patients without diuretics. C_{Na} decreased after LTOT in six patients with an increase in $PaCO_2$ >6%, but C_{Na} increased in four patients with unchanged or decreased $PaCO_2$ following LTOT. *Conclusions:* Renal function (including filtration fraction) is impaired in hypoxaemic COPD. Filtration fraction is decreased following 6 months of LTOT solely in patients with severe pretreatment hypoxaemia and sodium clearance seems to be increased if improved oxygenation is not accompanied by increased $PaCO_2$.

doi:10.1053/rmed.2002.1401, available online at http://www.sciencedirect.com

Keywords renal function; inuline clearance; para-amino-hippurate clearance; lithium clearance; sodium clearance; filtration fraction; nocturnal hypoxaemia; long-term oxygen treatment; chronic obstructive pulmonary disease; hypercapnia.

INTRODUCTION

Water and salt retention eventually resulting in oedema formation is a frequently occurring feature in severe chronic obstructive pulmonary disease (COPD) (1). Oedema formation is more common during exacerbations of COPD (2). Exacerbations are associated with impaired arterial blood gases, increased pulmonary pressures and increased afterload of the right ventricle of the heart (2). However, at least in stable severe COPD, oedema formation may be noticed irrespective of the concurrence of pulmonary hypertension and decreased right ventricular cardiac function (3). Impaired renal function, particularly renal vasoconstriction leading to diminished renal plasma flow (RPF), has therefore been implicated as an additive factor for the oedema formation in COPD (4,5). Hypercapnia has in some studies been noticed as the only decisive factor leading to renal dysfunction in COPD (1,6,7). On the other hand, in other studies hypoxaemia, air flow obstruction or hormonal alterations such as increased catecholamine or endothelin production have been considered to be at least partially accountable for the renal vasoconstriction and reduced RPF in COPD (8,9). However, other renal functions, as for example glomerular filtration rate (GFR) or the salt load delivered to the distal tubules (10) may be affected by blood gas

Received 8 April 2002, accepted in revised form 24 June 2002
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aberrations and it may therefore be of importance to assess such functions.

Nocturnal hypoxaemia in COPD is associated with increased nocturnal catecholamine excretion (11) as well as daytime pulmonary hypertension (12). Nocturnal hypoxaemia in other diseases as for example obstructive sleep apnoea is associated with various hormonal alterations as well as altered renal excretion of salt and water (13,14). To our knowledge, there has been no report on the possible relationship between nocturnal hypoxaemia in COPD and daytime renal function.

The effects of improved oxygenation on renal function in COPD has only been investigated in short-term studies (4,5,10), despite that prospective studies of oxygen therapy imply that the beneficial effects on, for example, pulmonary circulation are more obvious after long-term oxygen therapy (LTOT) than after acute oxygen supplementation (15).

The aim of the present study was to investigate renal function in severe COPD patients with varying degrees of air flow obstruction and daytime blood gas impairments. The renal function was related to forced expiratory volumes, daytime blood gases and to the level of nocturnal hypoxaemia. A subgroup of the patients was subjected to at least 4 months of LTOT and a further aim was to study the possible long-term effects on renal function associated with the post-treatment improvement of daytime and nocturnal oxygenation.

SUBJECTS

Nineteen patients (10 males) who all suffered from moderate to severe airway obstruction (forced expiratory volume in 1 s (FEV_1) in percentage of predicted (%P) $<70\%$ and FEV_1/forced vital capacity (FVC) $<65\%$) were included in the study. All patients were investigated with regard to their possible need for LTOT. Four patients were considered not hypoxaemic enough to receive LTOT ($PaO_2 > 8.5$ kPa). The patients ($n=15$) who were deemed eligible for LTOT had quit smoking at least 4 weeks prior to the start of the study. These 15 patients had an arterial oxygen tension (PaO_2) <7.3 kPa while breathing ambient air ($n=5$) *or* a PaO_2 of 7.3–7.9 kPa ($n=7$) *or* PaO_2 of 8.0–8.3 kPa ($n=3$) but with substantial nocturnal hypoxaemia (arterial oxygen saturation (SaO_2) $<90\%$, lasting $>25\%$ of the nocturnal recording) in association with previous episodes of oedema. However, one hypoxaemic patient moved to another area, another one declined oxygen treatment and in yet another one, LTOT was discontinued due to subsequently improved oxygenation on air breathing. Thus, the 12 remaining hypoxaemic patients were investigated both before and after at least 4 months of LTOT (Table 1).

Five of the 19 patients had $PaCO_2$ levels above 6.5 kPa (range 6.7–7.9 kPa) and the rest had $PaCO_2$ values <6.5 kPa while breathing ambient air. All 19 patients except one had serum creatinine levels below the upper reference limit of our laboratory (120 μmol/l) and all patients

Table 1. Antropomorphic, lung function, gas exchange data in 19 COPD patients before LTOT and in 12 patients before and after 6 months of LTOT

	Before LTOT ($n=19$)	Before LTOT ($n=12$)	After LTOT ($n=12$)
BMI (kg/m^2)	22.7 ± 4.4	23.0 ± 4.1	22.4 ± 4
Hb (g/l)	146.6 ± 13.1	151.4 ± 10.6	146.3 ± 8.2
Pulse (beats/min)	84.5 ± 12.0	85.3 ± 10.5	82.5 ± 11.1
MAP (mmHg)	92.0 ± 13.0	93.8 ± 15.9	89.8 ± 12.6
FEV_1 (%P)	25.6 ± 14.6	28.5 ± 17.9	28.2 ± 16.5
FVC (%P)	52.5 ± 23.3	60.3 ± 27.3	60.7 ± 24.6
FEV_1/FVC (%)	39.0 ± 9.4	37.5 ± 11.3	37.7 ± 14.6
PaO_2 (kPa)	7.63 ± 1.08	7.29 ± 1.07	9.14 ± 0.74***
$PaCO_2$ (kPa)	5.98 ± 0.85	5.89 ± 0.89	6.25 ± 0.81
pH	7.41 ± 0.04	7.42 ± 0.04	7.40 ± 0.02
$MnSaO_2$ (%)	87.7 ± 2.8	87.1 ± 2.9	93.6 ± 2.2***
Nadir SaO_2 (%)	76.3 ± 7.7	76.6 ± 8.5	82.7 ± 4.8*
%*t* $SaO_2 < 90\%$	63.1 ± 27.9	70.6 ± 25.5	8.3 ± 14.7***
%*t* $SaO_2 < 85\%$	11.6 ± 18.6	12.0 ± 19.6	0.6 ± 1.2**

Abbreviations: BMI=body mass index; Hb=haemoglobin; MAP=mean arterial pressure; FEV_1=forced expiratory volume in 1 s; FVC=forced vital capcity; PaO_2 and $PaCO_2$= arterial tension of oxygen and carbon dioxide; $MnSaO_2$: mean arterial oxygen saturation during a nocturnal recording; %*t* $SaO_2 < 90$ and $<85\%$=cumulative time spent with $SaO_2 < 90$ and $<85\%$ in percentage of the nocturnal recording. Note that blood gases and oxygen saturation after LTOT were all taken during ongoing oxygen supplemenatation. Significantly different post-treatment levels compared to values before LTOT: *, **, ***=$P < 0.05, <0.01, <0.001$.

were in a stable cardiopulmonary state (as judged by comparisons with previous pulmonary X-rays, dynamic spirometries and electrocardiograms) at the time of the study. One patient had moderately elevated mean arterial pulmonary pressure (40 mmHg) because of moderate COPD combined with a previous episode of lung embolism. Twelve of the 19 patients used furosemide 40–120 mg/day because of previous episodes of oedema and 11 medicated with slow-release theophylline preparations. Eight of the 12 subjects who were investigated after at least 4 months of LTOT medicated with oral theophylline.

The patient's levels of inulin (In) and para-amino-hippuric acid (PAH) clearance were compared with those of 24 healthy normotensive males (all aged 63 years) who have been described previously (16). Although, our patients were significantly older (68.7 ± 0.6 years) than these healthy subjects the difference amounted to only 6 years. The other renal parameters were compared with the mean levels of corresponding parameters in two populations of young healthy subjects with a mean age of 32 and 34 years respectively (17,18).

The study was approved by the ethical committee of Huddinge University hospital and all patients gave their informed consent to participate in the study.

METHODS

Following a physical examination, venous samples were drawn for assessment of haemoglobin, creatinine and electrolytes using routine laboratory methods. Forced expiratory volumes were measured by dynamic spirometry (Vitalograph®, Buckingham, England) in the afternoon about 30 min after β_2- stimulation. The best of three assessments of FEV_1 was used for statistical analysis and FVC as well as the ratio between the two (FEV_1/FVC) was taken from that measurement.

A nocturnal finger pulse oximetry (Radiometer A/S, Copenhagen, Denmark) was executed the following night without oxygen supplement. Mean arterial oxygen saturation for the whole night ($MnSaO_2$) was calculated and the cumulative time with an SaO_2 level <90 and $<85\%$, respectively, in percentage of the total nocturnal recording time was estimated. Systemic blood pressure was measured while the patient was resting in bed at ca 06.00 a.m. Arterial blood gases (ABL 520, Radiometer A/S) were drawn with the patient resting in a semirecumbent position at 06.00–07.00 in the morning following the nocturnal pulse oximetry.

All oximetry tracings were scrutinised manually by the same observer (MR) without knowledge of the outcome of the renal functional studies.

Twelve hours before the renal clearance tests, the patients received 16.2 mmol of lithium carbonate (Li) orally. After an overnight fast (the same night the oximetry was performed) each patient drank 500 ml of water and then the urinary bladder was emptied. Thereafter starting at 08.00 h a.m. the patient drank 7.5 ml/kg body weight of water/h during 3 h. During this time the patient received infusions of 25% inulin (Inutest®, Kemiflour, Stockholm, Sweden; after a priming dose of 0.2 ml/kg body weight, a constant infusion of 0.5 ml/min was given) and 20% para-amino hippuric acid (Merck Sharp and Dohme, West Point, U.S.A.; after a priming dose of 0.03 ml/kg body weight, a constant infusion of 0.5 ml/min was given). The levels of In, PAH, lithium and sodium were assessed in plasma and in urine, and the mean of plasma levels taken at the beginning and the end of a 45 min period as well as the urinary level of the 45 min period was used for clearance calculations (18). Finally, the mean value of four 45 min sampling periods (i.e. 3 h) was used for statistical analysis. The clearance (C) of a substance was calculated by the formula: C=urinary level $\times$ volume/plasma level and corrected for 1.73 m^2 of body area. The filtration fraction (FF) was estimated by C_{In}/C_{PAH}. The salt and water load to the proximal and indirectly to the distal renal tubule and thus, the sodium reabsorption within the proximal and distal tubules can be accurately assessed by measuring the clearance of orally supplemented lithium (C_{Li}) (19).

The fractional and absolute levels of proximal sodium reabsorption were calculated by $1-(C_{Li}/C_{In})$ 100% and P_{Na} ($C_{In} - C_{Li}$) (mmol/min), respectively. The fractional and absolute levels of distal sodium (Na) reabsorption were calculated by $1-(C_{Na}/C_{Li})$ 100% and P_{Na} ($C_{Li} - C_{Na}$) (mmol/min) (17,18).

All of these measurements were repeated in 12 patients following 6.2 ± 0.9 months of LTOT. The oral medication was kept unaltered and the patient's ordinary diet was continued throughout the study period. At the second measurement, the nocturnal oximetry and the morning (at 06.00 a.m.) blood gases were performed during ongoing oxygen supplementation. Oxygen supplementation was discontinued at 07.45 a.m. The renal clearance tests were performed during ambient air breathing between ca 08.30 and 11.30 a.m. both before and after six months of LTOT.

STATISTICAL ANALYSIS

Parametric and non-parametric tests were used according to distribution. Results were presented as mean $\pm$ SD. Correlations between variables were assessed by linear regression (r) or by spearman rank correlation (r_s). Changes over time were determined by Student's paired t-test or Wilcoxon's signed-rank test. The change following treatment in the individual level of a parameter was estimated by the ratio between the value after 6 months of LTOT and the pretreatment value and was expressed as the Δ-value. Differences between groups were determined by Student's unpaired t-test or by Mann–Whitney

U-test. Differences between subgroups of less than 10 subjects were exclusively determined by Mann–Whitney U-test. The importance of different variables for the variability of a dependent parameter was determined by stepwise regression. *P*-values below 0.05 were considered significant.

RESULTS

Before LTOT (n=19)

Lung function and blood gas data are given in Table 1. All but two of the 19 patients had severe airway obstruction with an FEV_1 (%P) $<40\%$. Mean PaO_2 was 7.63 ± 1.08 kPa. Fourteen of the 19 patients had a $PaO_2 < 8.0$ kPa. All but five patients had a $PaCO_2 < 6.5$ kPa with, mean level 5.98 ± 0.85 kPa. In 84% of the patients the MnSaO_2 was $<90\%$ and about 3/4 of the patients spent more than 50% of the nocturnal recording with an SaO_2 below 90%, but only 20% of the patients spent more than 10% of the night with an $SaO_2 < 85\%$. Although 74% of the patients had a resting pulse of at least 80 beats/min, their mean arterial blood pressure was slightly and non-significantly lower (92.0 ± 13.0 mmHg) compared to that of the 63-year-old healthy individuals (97.8 ± 7.4 mmHg). Six patients were underweight ($BMI < 20\ kg/m^2$) and only two were obese ($BMI > 30\ kg/m^2$).

Renal function data are given in Table 2. C_{In} was $35 \pm 19\%$ and C_{PAH} was $48 \pm 19\%$ lower than the corresponding clearances in the 63-year-old normal controls. On the other hand, FF was $31 \pm 31\%$ higher than in the controls (16).

C_{Li}, the absolute proximal (APR) and distal sodium reabsorptions (ADR), the fractional proximal sodium reabsorption (FPR), as well as sodium clearance were significantly lower than the mean level of these parameters in young healthy individuals (17,18), whereas, the fractional distal sodium reabsorption (FDR) did not differ significantly from the mean level in healthy controls.

The 12 patients using diuretics had significantly higher theopylline dosage, but lower urinary volume, C_{Na} and FDR than patients without diuretic treatment (Table 3). The 11 patients using theofylline did not differ from the seven subjects without this medication with regard to renal clearance measurements.

Correlations

There was a weak negative correlation between MnSaO_2 and FF (Fig. 1) and increasing haemoglobin levels were associated with increasing FF levels ($r=0.52$; $P<0.05$). FEV_1%P correlated negatively with FDR ($r_s=-0.49$; $P<0.05$). Nocturnal time with $SaO_2<90\%$ correlated positively with pulse rate ($r_s=0.66$; $P<0.05$). C_{Li}, ADR and total urinary volume increased with increasing MAP (r-values ranging between 0.54 and 0.58; $P<0.05$ for all). C_{Na} was negatively correlated with FDR ($r_s=-0.75$, $P<0.01$). FPR was positively correlated with C_{In}, but inversely correlated with C_{Li} ($r_s=0.63$ and -0.79; $P<0.01$ and <0.001 resp.). Stepwise regression showed that 67%

TABLE 2. Renal function, salt and water excretion in 19 COPD patients before LTOT and in 12 patients before and after 6 months of LTOT as well as in healthy controls

	Before LTOT ($n=19$)	Before LTOT ($n=12$)	After LTOT ($n=12$)	Controls ($n=24$)
C_{In} (ml/min)	64.8 ± 17.7***	65.7 ± 16.7***	63.7 ± 14.2***	101.3 ± 21.0
C_{PAH} (ml/min)	243.4 ± 69.2***	242.0 ± 64.2***	249.3 ± 54.4***	491.4 ± 108.0
FF (%)	26.5 ± 4.3***	26.9 ± 5.1***	25.8 ± 3.7**	20.8 ± 3.5
C_{Li} (ml/min)	23.1 ± 8.5**	22.6 ± 9.4**	22.3 ± 8.2***	29.5
APR (mmol/min)	5.8 ± 2.7***	6.0 ± 2.5***	5.8 ± 1.9***	12.2
FPR (%)	61.9 ± 17.0**	64.1 ± 17.0**	63.3 ± 16.6**	74.3
ADR (mmol/min)	3.1 ± 1.2**	3.0 ± 1.3**	3.0 ± 1.1**	3.9
FDR (%)	94.8 ± 1.9	94.9 ± 2.0	95.0 ± 2.5	94.6
S-creatinine (μmol/l)	88.1 ± 13.4	91.3 ± 14.8	91.1 ± 12.5	$<120^{ref.}$
P-sodium (mmol/l)	140.3 ± 4.9	140.6 ± 5.3	139.9 ± 5.1	
U-sodium (mmol/l)	31.6 ± 12.0	29.2 ± 10.5	25.1 ± 10.2	
U-volume (ml)	1080 ± 431.3	1112.6 ± 497.8	1186.6 ± 332.7	
C_{Na} (ml/min)	1.23 ± 0.69*	1.12 ± 0.78*	1.06 ± 0.57***	1.6

Abbreviations: *C*=clearance; In=inulin; PAH=para-amino-hippuric acid; FF=filtration fraction; Li=lithium; A=absolute; F=fractional; PR=proximal sodium reabsorption, DR=distal sodium reabsorption; Na=sodium. *, **, ***=$P<0.05$, <0.01, <0.001 regarding significant differences with regard to renal functional parameters between patients and healthy individuals. Note that after the first three parameters, only comparisons to the mean levels in the controls have been performed. Regarding the different control groups, see text. Ref.=upper reference limit.

Table 3. Significant differences regarding parameters before treatment (I) between patients treated with diuretics ($n=12$) and patients without this treatment ($n=7$) and the percentage of change (Δ) in variables following LTOT compared to the levels prior to LTOT, in patients on treatment with diuretics ($n=8$) and without diuretics ($n=4$)

	Diuretics	Non-diuretics
C_{Na} (ml/min) (I)	0.93 ± 0.46*	1.74 ± 0.75
U-volume (ml) (I)	904 ± 394*	1381 ± 326
FDR (%) (I)	95.6 ± 1.6*	93.4 ± 2.0
Standard bicarb. (mmol/l) (I)	27.7 ± 1.3*	26.0 ± 1.5
P-albumin (g/l) (I)	44.6 ± 4.4*	35.8 ± 2.9
$\Delta FEV_1/FVC$ (%)	-12.5 ± 12.0*	17.1 ± 16.2
ΔC_{Na} (%)	36.5 ± 61.0*	-42.5 ± 16.7

Abbreviations: see Tables 1 and 2. *$P<0.05$ regarding differences between the two patient subgroups. A positive Δ-value denotes an increased level and a negative Δ-value denotes a decreased level following LTOT.

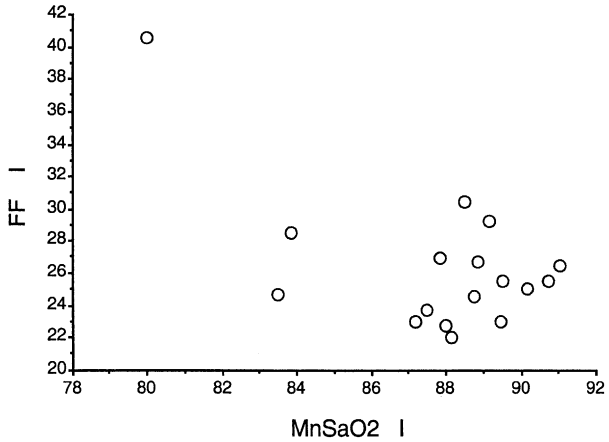

Fig. 1. Correlation between pretreatment levels of mean nocturnal SaO_2 ($MnSaO_2$ I) and of filtration fraction (FF I) ($r=-0.59$; $P<0.05$, using simple regression).

of the variability in FPR before LTOT could be explained by C_{Li} and a further 27 % could be determined by C_{In}.

During LTOT (n=12)

$MnSaO_2$ and daytime PaO_2 measured during ongoing oxygen supplement increased significantly by $7.8 \pm 2.8\%$ and by $27 \pm 22\%$ respectively following 6.2 ± 0.9 months of LTOT. In all but one patient $MnSaO_2$ exceeded 90% and all but one patient spent less than 25% of the nocturnal recording with an SaO_2 <90% and in all 12 patients daytime PaO_2 exceeded 8.0 kPa during ongoing oxygen supplement with a mean flow of 1.5 ± 0.7 l/min. All but one patient used the oxygen supplement for at least 16 h/day. Neither $PaCO_2$, forced expiratory volumes nor BMI, pulse rate or blood pressure changed significantly after treatment. MAP was now significantly lower than in 63-year-old controls. Haemoglobin and serum creatinine levels remained unaltered (Table 1).

FEV_1/FVC declined in patients using diuretics, but increased in patients without this treatment (Table 3). Despite this finding, $PaCO_2$ did not change significantly ($1 \pm 8.5\%$) in those on diuretics, while it increased by $11.5 \pm 5.4\%$ ($P<0.05$ (paired t-test)) in four subjects without this treatment.

Renal function as assessed by the clearance measurements and sodium and water excretion (measured without oxygen supplement) remained unchanged following 6 months of LTOT (Table 2). Sodium clearance increased in patients on diuretics but C_{Na} was reduced in patients without this therapy (Table 3).

Blood gases taken during ongoing oxygen supplement showed that in six patients $PaCO_2$ increased by more than 6% during LTOT and in four this parameter decreased or remained unaltered (one patient, in whom the increase in $PaCO_2$ did not exceed 6% and another patient in whom $\Delta PaCO_2$ could not be determined, were not included in the following subgroup comparison). In those patients where $PaCO_2$ increased, LTOT was associated with a fall in C_{Na}. Conversely C_{Na} increased following LTOT in the other subgroup. Furthermore, the post-treatment levels of FDR and daytime PaO_2 were elevated, whereas the levels of urinary sodium concentration and nadir nocturnal SaO_2 were lower in the subgroup with increased $PaCO_2$ compared to other subgroup (Table 4).

Correlations

Although, LTOT did not bring about any significant changes regarding certain parameters for the entire study group, individual changes (Δ-values) regarding these parameters, could be highly and significantly correlated. Patients with low $MnSaO_2$ before LTOT experienced large post-treatment decrements in FF, while FF *increased* in those with relatively high $MnSaO_2$ prior to LTOT (Fig. 2). The change in FF induced by LTOT

Table 4. Significant differences regarding variables after ≥4 months of LTOT (II) and the percentage of change in parameters following LTOT (Δ-value), between patients with an increase of more than 6% in $PaCO_2$ (n=6) and patients with unaltered or reduced $PaCO_2$ (n=4) during ongoing oxygen supplementation

	$\Delta PaCO_2$ >6%	$\Delta PaCO_2$ <0%
U-sodium (mmol/l) (II)	18.3 ± 5.8**	35.0 ± 8.5
PaO_2 (kPa) (II)	9.49 ± 0.77**	8.52 ± 0.13
Nadir O_2 (%) (II)	80 ± 4.6*	87 ± 2.6
FDR (%) (II)	96.1 ± 1.6**	92.5 ± 1.8
ΔC_{Na} (%)	−31 ± 39**	55 ± 60
ΔFDR (%)	1.8 ± 1.8**	−22.3 ± 2.8

Abbreviations: See Tables 1 and 2. *, **=P=0.05, <0.05 regarding differences between the two patient subgroups.

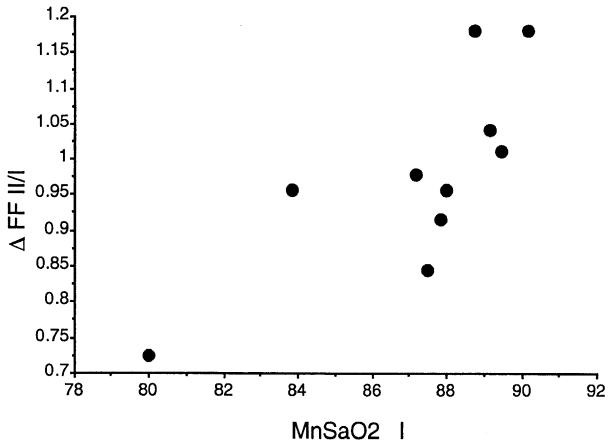

Fig. 2. Spearman rank correlation between pretreatment levels of mean nocturnal SaO_2 ($MnSaO_2$ I) and the post-treatment change (increase is denoted by values > 1.0 and decrease by values < 1.0) in filtration fraction (ΔFF II/I) (r=0.73; P < 0.05).

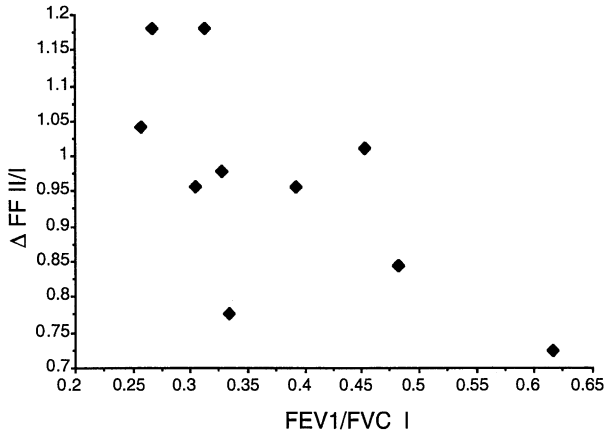

Fig. 3. Spearman rank correlation between pretreatment FEV_1/FVC I and the post-treatment change (increase is denoted by values > 1.0 and decrease by values < 1.0) in filtration fraction (ΔFF II/I) (r=−0.71 ; P < 0.05).

correlated inversely to pretreatment FEV_1/FVC (Fig. 3). $MnSaO_2$ level during oxygen supplement correlated positively with the change in FF following 6 months of LTOT (r_s=0.70; P < 0.05). The level of PaO_2 during LTOT was positively related to FDR and to S-creatinine, but negatively related to C_{Na} during LTOT (r=0.62, 0.56 and −0.65; P < 0.05 for all). The LTOT-induced increments in $MnSaO_2$ correlated with increased FDR (r=0.67; P < 0.05). The post-treatment increase in PaO_2 levels was associated with a reduction in C_{PAH} (r_s=−0.73; P < 0.05).

$\Delta PaCO_2$ levels (measured during ongoing oxygen supplement) following LTOT correlated positively with post-treatment ΔS-creatinine (r_s=0.83, P < 0.05). Individual changes in FEV_1/FVC and MAP were inversely correlated (r=−0.84; P < 0.01). Likewise, ΔFF correlated positively with ΔC_{In} (r_s=0.81; P < 0.02).

DISCUSSION

The main findings in the present study are that patients with hypoxaemic COPD have severe impairments of renal function, despite normal serum creatinine levels. Renal function, assessed as filtration fraction is improved following LTOT, solely in patients with severe nocturnal hypoxaemia prior to oxygen treatment. This is to our knowledge the first study to demonstrate the long-term effects of oxygen therapy in COPD. Moreover, by measuring C_{Li} (19) the reabsorption of sodium in both the proximal and indirectly in the distal tubules could for the first time be described in hypoxaemic COPD.

The patients in the present study are quite representative for patients with stable severe chronic airway obstruction. The patients had a wide range of PaO_2 levels but only few had substantially increased $PaCO_2$ levels. No patient had severe oedema of the lower extremities at the time of the study, but 2/3 of the subjects were continuously treated with diuretics because of previous episodes of oedema. In an outlier who also suffered from pulmonary hypertension (see subjects) FF was substantially elevated [to 40.5% (Fig 1)]. His pulmonary hypertension may have affected other vascular systems including the renal microvasculature (20). Our patients continued their ordinary medication and diet until the night before

the clearance measurements. In other studies, all oral medication has been discontinued and the patients have been subjected to a standardised diet for 3 days before commencement of the renal functional study (1,10,21,22). However, the effects *per se*, of such abrupt changes are unclear. Furthermore, our intention was to clarify the value of renal clearance measurements in normal clinical practice.

Other researchers have contended that the clearance methods used in the present study, for example PAH clearance, are unreliable in diseased states as COPD (6). However, simultaneous measurements in COPD patients regarding the acute effects of oxygen on renal plasma flow using Doppler ultrasound and PAH clearance have shown reasonably good correlation between the two methods and that both methods seem to accurately reflect changes in renal function (5). Furthermore, the clearance assessments in the present study were most probably reliable, given that both water intake and urinary production were closely supervised and that more than 90% of each of the 45 min sampling periods were properly carried out.

Despite the normal serum creatinine levels, all renal clearance measurements including GFR and renal plasma flow were severely diminished in our study. Reduced muscle mass due to ageing and COPD probably contributed to the preservation of the normal creatinine levels (23,24). The expected inverse relationship (11) between fractional proximal sodium reabsorption (FPR) and C_{Li} was noted in our patients both before and after treatment. However, FPR was also dependent on GFR, and GFR was more severely impaired compared to C_{Li} (mean reduction compared to controls: 35% *vs.* 22%). The reduced GFR probably contributed to the reduction in sodium load being delivered to the distal part of the proximal tubules (i.e. C_{Li}), which in turn reduced the *absolute* reabsorption of sodium from both the proximal and distal tubules. On the other hand, the reduced absolute sodium reabsorption could partially have been counteracted by increased aldosterone levels, which tends to raise the sodium reabsorption from the distal tubuli (8,1) and the net result may be a predominant reduction in the *fractional* sodium reabsorption from the proximal tubuli as found in our study.

There were weak correlations between increased FF on the one hand and severity of pretreatment nocturnal hypoxaemia and secondary polycythaemia on the other. However, there was no correlation between daytime blood gas aberrations and renal dysfunction, thus suggesting that nocturnal physiological alterations may sometimes be of greater importance than diurnal ones for the development of daytime physiological impairments (11,12,25). Like in previous studies (5,10,22) we found that the elevated FF was due to a more pronounced reduction in renal plasma flow (i.e. C_{PAH}) than in glomerular filtration (C_{In}). The elevated FF is probably reflecting increased renal vascular resistance, possibly in turn due to efferent renal arteriolar vasoconstriction (5,9,22). However, this vasoconstriction was alleviated solely in subjects with severe pretreatment nocturnal hypoxaemia (including the above-mentioned outliner) (Fig. 2). This finding may imply that factors other than hypoxaemia are of importance for the renal efferent arteriolar vasoconstriction. First of all, studies in healthy subjects imply that increased breathing effort in itself may alter renal blood flow (26). Severe chronic airflow obstruction and hyperinflation is accompanied by increased basal inspiratory pressure and thus, probably elevated work of breathing (27).

Second, severe airway obstruction is associated with elevated end-expiratory alveolar pressure, in turn associated with decreased venous return and oedema formation of the lower extremities (28). In several studies of COPD patients, it has been found that degree of impaired renal function is related not only to blood gas disturbances, but also to the severity of airflow obstruction (1,8,22). The patients in our study with the most severe air flow obstruction had the most elevated post-treatment FF.

Third, the reduced venous return may be counteracted by altered baro-receptor reflexes, which possibly in conjunction with increased catecholamine secretion will lead to increased pulse rate which in turn will prohibit a severe decrease in systemic vascular pressures. Thus, a further fall in salt delivery to the renal tubules and urinary output will be prevented (8,12). In our study increasing MAP was associated with increases in C_{Li} and in urinary volume and neither MAP nor pulse rate was altered by LTOT.

Fourth, already mild to moderate hypercapnia may contribute to renal vasoconstriction, as has been noted in the present and in previous studies of COPD patients (8,22).

Fifth, chronic air flow obstruction as well as impaired gas exchange may give rise to numerous hormonal abnormalities. These may consist of increases in sympathetic nervous norepinephrine (NE) secretion (11), endothelin production (9), plasma renin activity, aldosterone and antidiuretic hormone secretion (1,8) as well as reduced production of atrial natriuretic peptide (ANP) (21) and possibly of diminished renal NO production (29). The importance of all of these factors for the long-term evolution of renal function in severe hypoxaemic COPD is largely unknown. Long-term treatment with ACE inhibitors in order to decrease the renal vascular pressures seems not to be beneficial for the renal function in severe COPD (30). Nevertheless, LTOT for at least 4 months reduces NE excretion but only if the nocturnal oxygenation is substantially improved (11). Whether there exists an association in COPD between NE excretion and renal vasoconstriction, assessed by increased filtration fraction, remains to be elucidated.

Finally, in hypoxaemic COPD, the balance between renal oxygen delivery and renal oxygen consumption may be severely disturbed and, thus, aggravated kidney tissue hypoxia may ensue (31).

Intravenous infusions of theofylline might increase natriuresis (32) but, long-term oral theophylline treatment seems to be of little consequence for sodium excretion (33). In the present study, the sodium clearance and the other clearance measurements did not differ significantly between those treated with slow-release theophylline and those without theophylline.

Treatment with diuretics seems to be rather related to the severity of airway disease (21) as judged by the higher use of theofylline and the continuous deterioration in airway obstruction in our subgroup on diuretic treatment compared to the patients without diuretics. Despite continuous treatment with diuretics, these patients, prior to LTOT, exhibited reduced ability to excrete a water load and their sodium clearance was probably antagonised by an elevated fractional distal tubular sodium reabsorption (FDR) rate. These findings should not be considered as indicating that treatment with diuretics in COPD patients with oedema is of no avail (22), since clinical experience, as well as several studies, has shown beneficial effects of diuretics on kidney function particularly in exacerbations of COPD (2). Continuous treatment with diuretics in our stable COPD patients was associated with unchanged $PaCO_2$ levels after 6 months of LTOT, whereas patients without diuretics exhibited raised $PaCO_2$ levels after LTOT. The increase in C_{Na} following LTOT in the subgroup treated with diuretics may suggest that normalisation of the arterial oxygenation is a prerequisite for achieving effective renal tubular salt and water excretion using loop diuretics (2).

Higher levels of diurnal and nocturnal oxygenation during LTOT were surprisingly enough associated with deterioration in renal function as manifested by raised post-treatment FF and FDR and diminished C_{Na}. Our findings are probably not due to a detrimental effect of the improved oxygenation in itself, but rather due to the harmful effect of a mean post-treatment increase in daytime $PaCO_2$ of 14% in half of our patients. In this subgroup of our patients a reduced C_{Na} and high post-treatment FDR were noted, whereas sodium clearance increased and FDR decreased in patients with decreased $PaCO_2$ during LTOT. Thus, even rather minor increments in $PaCO_2$ may impair the renal microcirculation (22). The choice of a cut-off point of $>6\%$ for the increase in $PaCO_2$ following LTOT was based on a previous study (34) showing that 6–8% is a common level for the increase in $PaCO_2$ in COPD patients given LTOT.

The elevated FDR in our hypercapnic patients suggests that such patients have smaller reserve capacity for excreting additional water and salt loads (6,8,22). In individuals with increased GFR following LTOT and thus increased influx of fluid and electrolytes, FF tended to increase, probably because the renal vasculature to a great extent remained in a constricted and rigid state.

The lower nadir nocturnal SaO_2 in the subgroup with post-treatment increments in daytime $PaCO_2$ may imply that this subgroup suffered from substantial alveolar hypoventilation (34), leading to substantial nocturnal hypercapnia (35).

In conclusion, hypoxaemic COPD patients have impaired renal function, demonstrated by reduced glomerular filtration rate, renal plasma flow and sodium clearance. The FF is elevated, probably due to vasoconstriction of efferent renal arterioles. Six months of LTOT is accompanied by a reduction in FF solely in patients with severe pretreatment nocturnal hypoxaemia. Post-treatment sodium clearance seems to be increased, given that the improved oxygenation is *not* accompanied by raised $PaCO_2$-levels.

Acknowledgements

We extend our gratitude to the nurses of the department of Renal Medicine for excellent assistance with the renal clearance measurements.

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